(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 002 259**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 78101491.5

(22) Date of filing: 01.12.78

(51) Int. Cl.²: C 07 D 233/86
C 07 D 403/00, A 61 K 31/41

(30) Priority: 01.12.77 GB 50093/77

(43) Date of publication of application:
13.06.79 Bulletin 79/12

(84) Designated contracting states:
BE CH DE FR GB IT LU NL SE

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(54) **Hydantoin derivatives and salts thereof, their synthesis and intermediates, and pharmaceutical formulations.**

(57) The invention relates to new thiohydantoin derivatives with pharmacological properties related to those of natural prostaglandins, intermediates therein, compositions containing the said derivatives, and their use in medicine. In particular, certain compounds have been found to be potent mimetics of the anti-platelet aggregatory properties of prostaglandin E_1.

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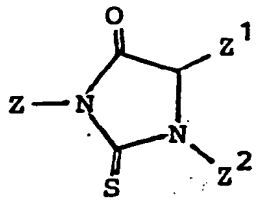
This invention relates to heterocyclic compounds, their synthesis, intermediates therein, compositions containing the heterocyclic compounds, and their use in medicine.

Thiohydantoin derivatives, defined hereinbelow in formula (I), have been found by the applicants to have pharmacological properties related to those of natural prostaglandins, as demonstrated by their ability to mimic or antagonise the physiological effects of the natural prostaglandins in various biological preparations. In particular, certain compounds of formula (I) have been found to be potent mimetics of the anti-platelet aggregatory properties of prostaglandin E_1.

In formula (I)



in which Z is hydrogen or alkyl;
one of Z^1 and Z^2 is represented by the group $-CH_2-X-X^1-X^2$
wherein X is phenylene, $-C\equiv C-$, cis or trans $-CH=CH-$ or $-CH_2-CQ_2-$
in which each Q is independently selected from hydrogen and alkyl, such as ethyl, (i.e. the carbon atom carrying the two Q groups may be substituted as

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follows: $-CH_2-$, $-CHQ^3-$ or $-CQ^3{}_2-$, in which Q^3 is alkyl, such as ethyl) or the two Q's together form an alkylene radical having four, five or six carbon atoms;

X^1 is a covalent bond or a straight or branched alkylene chain having 1 to 6 carbon atoms optionally having one of its methylene groups replaced by oxa(-O-) or thia(-S-) provided that at least one carbon atom separates the oxa or thia group from a $-C\equiv C-$, -CH=CH- or -CO- group; and

X^2 is selected from 5-tetrazolyl, carboxyl, carboxamide, hydroxymethylene and alkoxycarbonyl;

and the other of Z^1 and Z^2 is represented by the group $-Y-Y^1-Y^2-Y^3$

wherein Y is $-CR_2-CH_2-$

in which each R is independently selected from hydrogen and methyl;

Y^1 is carbonyl, ethylene, methylene substituted by hydroxyl or methylene substituted by hydroxyl and alkyl;

Y^2 is a covalent bond or straight or branched alkylene having 1 to 7 carbon atoms optionally substituted on the carbon adjacent Y^1 by one or two groups each of which may be alkyl or a cyclic radical,

Y^3 is hydrogen, hydroxy, alkoxy having 1 to 7, preferably 1 to 4, carbon atoms, a cyclic radical, phenyl, benzyl, phenoxy or benzyloxy, wherein each of phenyl, benzyl, phenoxy and benzyloxy may be substituted in the benzene ring by one or more groups selected from hydroxy, halogeno, nitro, amino, acylamino, alkenyl, alkoxy, phenyl and alkyl which may itself be substituted by one or more halogeno groups;

or Y^2 and Y^3 together from an alkyl group having 1 to 7 carbon atoms of which at least one hydrogen is replaced by fluoro;

or Y is a bond, $-CH_2-$, or $-CH_2.CH_2-$ and

Y^1, Y^2 and Y^3 taken together from a cycloalkyl or bi-

cycloalkyl group substituted by a hydroxyl group which preferably has three carbon atoms separating it from the hydantoin ring.

In formula (I), the term cyclic radical means the monovalent radical derived by loss of a ring hydrogen atom from a monocyclic or polycyclic compound having from 3 to 12 ring atoms selected from carbon, nitrogen, oxygen, and sulphur, which compound may be saturated or unsaturated and may be further substited by one or more alkyl groups, but excluding phenyl. Such cyclic radicals include cycloalkyl having 3 to 10 carbon atoms such as cyclopropyl, cyclopentyl, cyclohexyl and cyclooctyl, bicycloalkyl having 4 to 10 carbon atoms such as adamantyl or norbornanyl (bicyclo[2,2,1]heptyl), spiroalkanyl having 5 to 12 carbon atoms such as 2-spiro[3,3]heptyl, 1-spiro[4,4]nonane and 8-spiro[4,5]decane, cycloalkenyl having 4 to 10 carbon atoms such as 4-cyclopentene, heterocyclic radicals such as tetrahydrofuranyl and tetrahydropyranyl and heteroaryl radicals such as thienyl, furyl, pyridyl, pyrimidyl, thiazolyl, imidazolyl and diazepinyl. Included in the term cyclic radical are these wherein one or more hydrogen atoms are replaced by fluoro.

Unless otherwise stated, in formula (I) and other formulae in this specification alkyl moieties are selected from methyl, ethyl, propyl, butyl, pentyl and hexyl, including all isomers thereof i.e. having from 1 to 6 carbon atoms for example, in the definitions of Y^1 and Y^2 the alkyl groups are preferably methyl; and the alkyl moiety of alkoxycarbonyl is preferably methyl or ethyl. Similarly alkylene groups have 2 to 4 carbon atoms for example vinyl.

In a compound of formula (I) the bonding of the divalent phenylene group may be <u>ortho</u>, <u>meta</u> or <u>para</u>, and the oxa

or thia group is preferably adjacent the phenylene or when X is other than phenylene then X^1 may be $-CH_2-O-CH_2-$.

Included in the meaning of compounds of formula (I) are the salts corresponding to the carboxylic acids and tetrazoles when X^2 is carboxyl or tetrazolyl respectively, and the salts which may also be formed when Z is hydrogen. Particularly valuable salts for human medical purposes are those having a pharmaceutically acceptable cation such as ammonium or that of an alkali metal eg. sodium and potassium, an alkaline earth metal eg. calcium and magnesium, or an organic base, particularly an amine such as ethanolamine. Salts having non-pharmaceutically acceptable cations are included within the ambit of this invention as useful intermediates to pharmaceutically acceptable salts, or the acids or esters of formula (I).

Except when there is clear indication to the contrary, formula (I) and other furmulae in the specification embrace all stereoisomers represented therein. In particular such formulae include the enantiomeric forms, such mixtures as are designated racemates, and diastereoisomers.

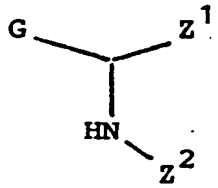
Preferably Z is hydrogen (or a salt thereof) and Z^1 is $-CH_2-X-X^1-X^2-$ as defined for formula (I).

The compounds of formula (I) wherein
Z is hydrogen or alkyl having 1 to 4 carbon atoms, for example methyl or butyl;
one of Z^1 and Z^2 is $-CH_2-X-X^1-X^2-$ wherein X and X^1 taken together form alkylene of 3 to 7 in particular 5 carbon atoms (including alkylene in which X is cis or trans $-CH=CH-$, i.e. X and X^1 form an alkylene radical) and X^2 is alkoxycarbonyl, carboxyl or a salt thereof;
and the other of Z^1 and Z^2 is $-Y-Y^1-Y^2-Y^3-$ wherein Y, Y^1

and Y^2 are as hereinbefore defined and Y^3 is hydrogen, phenyl, benzyl, or cycloalkyl or 4 to 7 carbon atoms; have particularly interesting prostaglandin-related properties. Within this definiton are included the subclass wherein Z is hydrogen or salt thereof and Z^1 is $-CH_2-X-X^1-X^2$ as defined.

The compounds of formula (I) maybe prepared by adapting methods known from the preparation of analogous compounds.

In particular, a convenient synthesis is by reacting a compound of formula (II)



(II)

wherein Z^1 and Z^2 have the same meaning as in formula (I) and G is a carboxyl group, alkoxycarbonyl, carboxamide or nitrile group with thiocyanic or alkyl iso thiocyanic acid or an alkylisothiocyanate as appropriate, depending on whether Z is hydrogen or alkyl respectively.

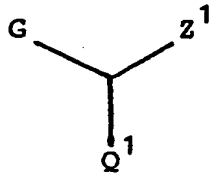
When thiocyanic acid is used, the acid is conveniently produced in situ by the use of an alkali metal thiocyanate, eg. potassium thiocyanate and ammonium thiocyanate, and an acid which may be present as an acid addition salt of the compound of formula (II) of a free acid of formula (II) wherein either or both of G and X^2 is carboxy. Alternatively an equivalent amount of mineral acid or an organic acid may be added to the reaction medium. The reaction may proceed in the absence of a solvent but preferably an inert solvent is used which is preferably polar such as water or a mixture of water with acetone, dimethylformamide, dimethylsulphoxide or a lower alkanol such as

ethanol or it may be non-polar such as a hydrocarbon, an ether or halogenated hydrocarbon such as chloroform. Where dosired, for example if no solvent is used, the reaction may be promoted by heating the reactants.

Similar reaction conditions may be used when an alkyl iso-thio cyanate is used except that it is unnecessary to provide an equivalent amount of acid, as an acid addition salt or otherwise, in the reactants.

Instead of using a thiocyanate or isothiocyanate, a compound of formula (II) may be reacted with thiourea, nitrothiourea or an N-alkylthiourea as appropriate. A solvent is not essential but if desired an inert solvent such as one mentioned above may be used, and the reaction is preferably effected at an elevated temperature, for example from 100° to 125°C but temperatures upto 150°C may be employed.

An intermediate of formula (II) may be conveniently prepared by reaction of a compound of formula (III) with a compound of formula (IV).



(III) $Q^2 - Z^2$ (IV)

wherein G, Z^1 and Z^2 are as defined in formula (III), one of Q^1 and Q^2 is amino and the other is halogeno, preferably bromo. The reaction may be carried out be heating in the absence of solvent or in the presence of an inert solvent such as ethanol.

The intermediates of formula (II) wherein Z^2 is $-Y-Y^1-Y^2-Y^3$ when Y^1 is carbonyl may also be prepared by reaction of an amine of formula (III) wherein Q^1 is amino with an unsaturated ketone of formula (V).

$$CR_2 = CH.CO.Y^2.Y^3 \qquad (V)$$

wherein R, Y^2 and Y^3 have the same meaning as in formula (I); the reaction being effected in the presence of absence of an inert solvent, and at room temperature or optionally with heating.

Tetrazoles of formula (I) (X^2 being 5-tetrazolyl) my be prepared from corresponding compounds wherein the group $-X^2$ is replaced by $-\underset{|}{\overset{X^4}{C}} = \underset{|}{\overset{X^3}{N}}$

wherein X^3 and X^4 together form a bond (nitrile), X^3 is hydrogen or alkyl and X^4 is alkoxy (imidoester), alkylthio (imidothioester), $-NH-NH_2$ (amidrazone), or amino (amidine) or X^3 is hydroxy and X^4 is amino (amidoxime). The reaction is preferably carried out in a polar aprotic liquid medium such as dimethylformamide using a salt of hydrazoic acid eg. sodium azide, However, when X^2 is replaced by an amidine or amidrazone, a suitable reagent is nitrous acid. If an amidine is reacted with nitrous acid then reduction of the intermediate nitrosation product, with or without prior isolation, using for example sodiumamalgam is required to give the corresponding tetrazole. The precursor to the tetrazole may be obtained by well known methods, for example the nitrile may be obtained by dehydration of the corresponding amide.

The alcohols of formula (I) wherein X^2 is hydroxymethylene may also be obtained by reduction with an appropriate reducing agent of the corresponding acid, ester, acid

halide, acid anhydride or aldehyde. The appropriate reducing agent will depend on the particular substrate, but reagent which may be used is sodium in ethanol. In particular a carboxylic acid may for example be converted to a corresponding mixed anhydride with ethylchloroformate in the presence of a base such as triethylamine, and subsequently reduced to the alcohol using sodium borohydride. Similarly an ester may be reduced to the alcohol using di-iso-butyl aluminium hydride in an inert solvent such as ether or hydrocarbon such as hexane or benzene. Such alcohols may also be prepared by catalytic hydrogenation.

Alternatively hydroxyl group-containing compounds of formula (I), expecially the alcohols wherein X^2 is hydroxymethylene may be prepared by hydrolysis of a corresponding halide with an appropriate reagent. For this purpose a hydroxide may be used for example an aqueous alkali or a suspension of sulver oxide in water.

In the synthesis of compounds formula (I) having a hydroxyl group in a side chain it may be desirable to protect this hydroxyl group during the course of the reaction. This may be readily effected in known manner using a protecting group such as acyl, aroyl, tetrahydropyran-2-yl, 1-ethoxyethyl or aralkyl, for example benzyl.

Removal of protecting groups may be carried out by appropriate methods known to those skilled in the art: for example an acyl group may be removed by acid or base hydrolysis, and a benzyl group by reductive cleavage.

Furthermore a ketone of formula (I) wherein Y^1 is carbonyl may be converted to the corresponding secondary alcohol by reduction with a suitable reducing agent, such as sodium borohydride. Also, an alcohol of formula (I) wherein Y^1

is -CH.OH- may be oxidised to the corresponding ketone using Jones' reagent, acid dichromate or any other suitable reagent.

Similarly where the compounds of formula (I) have a C ≡ C or CH = CH or -CH = CQ- link these may be converted by conventional hydrogenation techniques, for example using a Lindlar type or Adams catalyst, to the corresponding ethylenic or saturated compounds as appropriate.

The compounds of formula (I) have an asymmetric 5-carbon atom in the hydantoin ring and a further asymmetric centre is present in those compounds wherein Y^1 includes a hydroxyl group. Such alcohols therefore exist as four isomers which are separable by thin layer chromotography or high performance liquid chromatography into two diastereomers, each of which is a racemic mixture of two isomers. On separation of the diastereomers the less polar diastereomers being preferred, one diastereomer may be converted to a mixture of the four isomers by treatment with a base, such as an alkali metal hydroxide, and subwequently re-separated to provide two diastereomers. Repeated use of this technique enables the effectual conversion of one diastereomer to the other; this may be desirable when one diastereomer has a biological activity preferred to the other.

The corresponding alcohols of formula (II) or (III) also exist in four isomeric forms. If desired, these may be separated into two epimers and subsequent cyclisation to a compound of formula (I) retains the stereochemical configuration.

Other asymmetric centres can be present; for example if only one Q in formula (I) is other than hydrogen.

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In all of the foregoing chemical procedures it is of course evident that the choice of reactant will be dictated in part by the functional groups present in the substrate, and where necessary reactants having an appropriate selectivity of action must be used.

The compounds of formula (I) are of value in having pharmacological properties related to those of natural prostaglandins that is, the hydantoins mimic or antagonise the biological effects of members of the prostaglandin (PG) 'A', 'B', 'C', 'D', 'E' and 'F' series. For example, compounds of formula (I) have been found to mimic the antiaggregatory effect of PGE_4 on blood platelets, and to antagonise the contraction induced by PGE_2 or PGF_2 on smooth muscle taken from the rat stomach, rat colon, chick rectum and guinea pig trachea. In general, antagonistic properties, as opposed to mimetic, have been observed when using larger doses of the hydantoins. The pharmacological profile, by which is meant the relative activities, mimetic or antagonistic, compared with the natural prostaglandins, will of course vary depending on the specific hydantoin under consideration.

By reason of their prostaglandin-related properties, the compounds of formula (I) are useful in the pharmacological characterisation and differentiation of the biological activities of the natural prostaglandins and their 'receptors'. The further understanding of the physiological role of prostaglandins is of course valuable in the search for new and improved therapeutic substances.

The compounds of formula (I) are also of value of therapeutic agents. In particular compounds such as those described hereinbefore as having apotent anti-aggregatory effect on blood platelets are useful when it is desired

to inhibit platelet aggregation or to reduce the adhesive character of platelets, and may be used to treat or prevent thrombo-embolic disorders, e.g. the formation of thrombi in mammals, including man. For example, the compounds are useful in the treatment and prevention of myocardial infarcts, to treat and prevent thrombosis, to promote patency of vascular grafts following surgery, and to treat complications of arteriosclerosis and conditions such as atherosclerosis, blood clotting defects due to lipermia, and other clinical conditions in which the underlying aetiology is associated with lipid imbalance or hyperlipidemia. A further use for such compounds is as an additive to blood and other fluids which are used in artificial extra-corporeal circulation and perfusion of isolated body portions.

A group of compounds which have been found particularly valuable as inhibitors of platelet aggregation are those of formula (I) wherein Z is hydrogen; Z^1 is carboxyalkylene wherein the alkylene moiety has 3 to 9 carbon atoms; and Z^2 is a group $-(CH_2)_2.CH.OH.Y^2.Y^3$ wherein Y^2 is a bond or branched alkylene having a tertiary carbon atom adjacent the hydroxy-substituted carbon and Y^3 is as defined in formula (I). Within this group of compounds, those wherein Z^1 is carboxyhexyl or carboxyhexenyl and Y^3 is cycloalkyl having 4 to 7 carbon atoms have been found especially active.

It has also been found that compounds of formula (I) cause relaxation of vascular smooth muscle in a similar way as do members of the prc glandin 'A' and 'E' series. Compounds relacing vascular smooth muscle are capable of inducing vasodilation and therefore have antihypertensive properties and are useful in lowering blood pressure in mammals, including man, and may be used alone or in

combination with a ß-adrenoceptor blocking agent or another antihypertensive substance for the treatment of all grades of hypertension including essential, malignant and secondary hypertension.

Thiohydantoins of formula (I) also mimic the evvect of PGE_1 of antagonising histamine induced broncho-constriction, and such compounds may be used in the treatment or prophylaxis of bronchial asthma and bronchitis by alleviating the bronchoconstriction associated with this condition.

Thiohydantoins of formula (I), which inhibit pentagastrin-induced gastric acid secretion and reduce the formation or aspirin-induced gastric lesions in rats are useful in reducing excessive gastric secretion, reducing and avoiding gastro-intestinal ulcer formation and accelerating the healing of such ulcers already present in the gastro-intestinal tract whether such ulcers arise spontaneously or as a component of polyglandular adenoma syndromes.

Intravenous infusions of certain compounds of formula (I) to dogs will increase the urine volume indicating a potential utility for such compounds as diuretic agents, the uses of which include the treatment of oedema for example oedema associated with heart failure, liver failure or kidney failure in man or other mammals.

A further use for compounds of formula (I) which mimic the uterine smooth muscle effects of PGE_2 and PGF_2 is as anti-fertility agents, in particular as abortifacients.

In addition the compounds of formula (I) may be used in the treatment of proliferative skin diseases such as are associated with excessive cell division in the epidermis

or dermis which may be accompanied by incomplete cell differentiation. Particular conditions which may be alleviated include psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and swuamous cell carcin omas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun induced keratosis, non malignat keratosis, acne and seborrheic dermatitis in humans and atopic dermatitis and mange in domestic animals. For the treatment of these conditions the compound are desirably applied topically to the affected skin. Alternatively they may be administered by intradermal or intramuscular injection which may be directly into the skin lesion or into the surrounding tissue. Injectable compositions will generally contain from 0,1 to 0,5 % w/v of active ingredient.

The amount of a compound of formula (I) required to achieve the desired biological effect will of course depend on a number of factors, for example, the specific compound chosen, the use for which it is intended, the mode of administration, and the recipient. In general, a daily dose may be expected to lie in the range of from 1 µg to 20 mg per kilogram bodyweight. Preferably the daily dose is 10 micro g to 2 mg, especially 100 micro g to 0,2 mg (200 micro g), per kilogram bodyweight. For example, an intravenous dose may lie in the range of from 5 µg to 1 mg/kg, preferably 50 µg to 100 µg/kg, which my conveniently be administered as an infusion of from 0,01 to 50 µg and preferably 0,1 to 5 µg, especially 0,5 to 1 µg per kilogram per minute. Infusion fluids suitable for this purpose may contain from 0,001 to 100, for example from 0,01 to 10 µg per millititre. Unit doses my contain from 10 µg to 100 mg of a compound of formula (I), depending on how the compound is to be administered, for example ampoules for injection may contain from 0,01 to 1 mg,

preferably 0,05 to 0,15 mg, for example 0,1 mg, and orally administrable unit dose formulations such as tablets or capsules may contain from 0,1 to 50, preferably 2 to 20 mg, especially 5 to 15 mg, for example 10 mg.

More specifically, when a compound of formula (I) is used to inhibit platelet aggregation it is generally desirable to achieve a concentration in the appropriate liquid, whether it be the blood of a patient or a perfusion fluid, of about 1 ug to 10 mg, preferably from 10 ug to 1 mg, especially 0,05 to 0,15 mg, for example 0,1 mg, per litre.

The abovementioned doses refer to the acids, amides, esters, alcohols and tetrazoles of formula (I); where a salt is used, the dose should be taken as referring to the corresponding anion.

For use in the treatment or prophylaxis of the conditions referred to above, while the hydantoin compounds may be used as the raw chemical they are preferably presented with an acceptable carrier therefor as a pharmaceutical formulation. The carrier must of course be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The carrier may be a solid or a liquid, and is preferably formulated with a hydantoin compound as a unit-dose formulation, for example a tablet, which may contain from 0,05 % to 95 % by weight of the hydantoin compound. Other pharmacologically active substances may also be present in formulations of the present invention as indicated above. The hydantoin compounds may be incorporated in the formulations either in the form of the acid or the salt, ester (or amide) thereof, and the formulations may be prepared by any of the well-known

techniques of pharmacy consisting essentially of admixture of the components of the formulation.

The formulations include those suitable for oral, rectal, topical (buccal - eg. sub-lingual), the parenteral (that is subcutaneous, intramuscular and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated, and on the nature of the hydantoin compound.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets, lozenges or tablets each containing a predetermined amount of hydantoin compound; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; as an oil-in-water emulsion; or as a water-in-oil liquid emulsion. Such formulations may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the hydantoin compound with the carrier which constitutes one or mor accessory ingredients. In general they are prepared by uniformly and intimately admixing the hydantoin compound with liquid or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example a tablet may be prepared by compression or moulding a powder or granules of the hydantoin compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the hydantoin compound in a free-flowing form such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent(s). Moulded tablets may be made by moulding in a suitable machine the powdered hydantoin compound moistened with an inert liquid diluent.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a hydantoin compound in a flavoured basis, usually sucrose and acacia or tragacanth; and pastilles comprising a hydantoin compound in an inert basis such as gelatin and glycerin; or sucrose and acacia.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vasoline, lanoline, polyethylene glycols, alcohols and combinations thereof. The active ingredient is generally present in a concentration of from 0,1 to 15 % w/w of the composition, for example from about 0,5 to about 2 %.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of a hydantoin compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous or intramuscular injection. Such preparations may be conveniently prepared by admixing the hydantoin compound with water and rendering the product sterile and isotonic with the blood.

Formulations suitable for rectal administration are preferably presented as unit-dose suppositories. These may be prepared by admixture of the hydantoin compound with one or more of the conventional solid carriers, for example cocoa butter, and shaping of the resulting mixture.

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It will be appreciated from the foregoing that what we will claim may comprise any novel feature described herein, principally and not exclusively, for example:-

(a) The novel compounds of formula (I) as hereinabove defined.

(b) A method for the preparation of the novel compounds of formula (I) as hereinabove described.

(c) A pharmaceutical formulation comprising a compound of formula (I) in association with a pharmaceutically acceptable carrier therefor, and methods for the preparation of such formulations.

(d) A method for lowering blood pressure in a mammal including man which comprises administration to the mammal of an effective hypotensive, non-toxic amount of a compound of formula (I).

(e) A method for the treatment or prophylaxis of thrombosis in a mammal including man or mammalian including human, tissue which comprises administration of a non-toxic, effective anti-thrombotic amount of a compound of formula (I).

(f) A method for inducing vasodilation in a mammal, including man, comprising administration to said mammal of a non-toxic effective vasodilatory amount of a compound of formula (I).

(g) A method for the treatment or prophylaxis of gastric lesions in a mammal including man comprising administration to said mammal of a non-toxic effective prophylactic or therapeutic amount of a compound of formula (I).

(h) A method for inducing bronchodilation in a mammal, including man, comprising administration to said mammal of a non-toxic, effective bronchodilatory amount of a compound of formula (I).

(i) A method for the treatment or prophylaxis of an allergic condition in a mammal, including man,

comprising administration to said mammal of a non-toxic effective prophylactic or therapeutic anti-allergic amount of a compound of formula (I).

(j) A method of inducing abortion of a foetus in a mammal including man comprising administration to said mammal of a non-toxic effective abortifacient amount of a compound of formula (I).

(k) A method of inducing infertility in a mammal including man comprising administration to said mammal of a non-toxic effective contraceptive amount of a compound of formula (I).

(l) A method of treating a proliferative skin disease in a mammal which comprises bringing an effective therapeutic amount into contact with the skin lesion.

(m) A compound of formula (II), as defined hereinbefore, where novel.

The invention is illustrated by the following examples which should not be construed as a limitation thereof.

Example 1

5-(6-Carboxyhexyl)-1-(3-hydroxyoctyl)-2-thiohydantoin

Diethyl 2-[(3-hydroxyoctyl)amino]nonanedioate (26,6 g) was stirred with 2N hydrochloric acid (38 ml) at room temperature for 1 hour and the water was evaporated *in vacuo* to leave the desired hydrochloride salt.

A stirred mixture of diethyl 2-[(3-hydroxyoctyl)amino]-nonanedioate hydrochloride (29,0 g) with ammonium thiocyanate (5,6 g) was heated at 158° for 1,25 hours. The cooled reaction mixture was treated with water (200 ml), the product was extracted into chloroform (4 x 30 ml), and the chloroform solution was washed with water and

dried over magnesium sulphate. Evaporation of the chloroform yielded the cured 2-thiohydantoin ester. This ester (29,0 g) and 1N sodium hydroxide solution (130 ml) were stirred together at room temperature for 3 hours and neutral material was then removed with ether (2 x 40 ml). The aqueous alkaline phase was acidified with hydrochloric acid to pH 3, the liberated carboxylic acid was extracted into ether (4 x 50 ml) and the ethereal solution was washed with water and dried over magnesium sulphate. Evaporation of the ether yielded 5-(6-carboxyhexyl)-1-(3-hydroxyoctyl)-2-thiohydantoin as a mixture of 2 diastereomers which were separated by h.p.l.c. on SiO_2 in $CHCl_3$/MeOH/AcOH, 97,7 : 1,8 : 0,5. The individual diastereomers had relative r_f values of 0,61 (mor polar isomer) and 0,64 (less polar isomer) (SiO_2, $CHCl_3$/MeOH/HOAc, 90 : 5 : 5).

Example 2 to 8

By the method of Example 1 the following compounds:
diethyl 2-[(5,5-dimethyl-3-hydroxyhexyl)amino]nonanedioate;
diethyl 2-[(3-cyclohexyl-3-hydroxypropyl)amino]nonanedioate;
diethyl 2-[(3-(4-cis-methylcyclohexyl)-3-hydroxypropyl)amino]nonanedioate;
diethyl 2-[(3-cyclopentyl-3-hydroxypropyl)amino]nonanedioate;
diethyl 2-[(3-cyclohexyl-3-hydroxypropyl)amino]non-4-enedioate;
diethyl 2-[(3-cyclopentyl-3-hydroxypropyl)amino]non-4-enedioate;
and
diethyl 2-[(5,5-dimethyl-3-hydroxyhexyl)amino]non-4-enedioate;

were converted to the desired end products:

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5-(6-carboxyhexyl)-1-(5,5-dimethyl-3-hydroxyhexyl)-2-thiohydantoin, which was separated into two diastereomers one a colorless gum, the other a white crystalline solid m.p. 123 - 126°C;

5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl)-2-thiohydantoin which was separated into two diastereomers each of which was a colorless gum;

5-(6-carboxyhexyl)-1-(3-(4-cis-methylcyclohexyl)-3-hydroxypropyl)-2-thiohydantoin which was separated into two diastereomers each of which was a colourless gum;

5-(6-carboxyhexyl)-1-(3-cyclopentyl-3-hydroxypropyl)-2-thiohydantoin;

5-(6-carboxyhex-2Zenyl)-1-(3-cyclohexyl-3-hydroxypropyl)-2-thiohydantoin which was separated into two diastereomers one a colourless gum and theother a white crystalline solid m.p. 109 - 111°C;

5-(6-carboxyhex-2Zenyl)-1-(3-cyclopentyl-3-hydroxypropyl)-2-thiohydantoin; and

5-(6-carboxyhex-2Z-enyl)-1-(5,5-dimethyl-3-hydroxyhexyl)-2-thiohydantoin;

which was separated into two diastereomers, one an oild and the other a crystalline solid m.p. 102 - 105°C.

Example 9

5-(6-carboxyhexyl)-3-methyl-1-octyl-2-thiohydantoin

A solution of diethyl 2-octylamino azelate (7,44 g) and methyl iso thiocyanate (1,15 g) in dry ether (21 ml) was allowed to stand at room temperature for 48 hours, after which time the ether was evaporated to leave an oil which was hydrolysed to the desired hydantoin using 5N sodium hydroxide solution for 3 hours at room temperature. The product, a viscous pale yellow oil, was obtained by extraction from ether and purified by chromatography on a column of silica gel.

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Example 10

By a method analogous to that described in Example 9, but using ethyl 2-(6-ethoxycarbonylhexylamino)decanoate as starting material, there was obtained 1-(6-carboxyhexyl)-3-methyl-5-octyl-2-thiohydantoin as a pale yellow oil.

Example 11

Interconversion of diastereomers

A solution of the hydantoin diastereomer to be converted is prepared in N-sodium hydroxide solution and allowed to stand at room temperature for several hours. The solution is then acidified and extracted with ether, and the ether extract is washed with water, dried and evaporated.

By means of high performance liquid chromatography the product remaining may be separated into two diastereomers; one identical with the starting material and the other being the other (second) diastereomer.

In similar fashion, the second diastereomer may converted into a mixture of approximately equal quantities of itself with the first diastereomer, and the pure diastereomers isolated by means of high performance liquid chromatography.

Example 12

Inhibition of Platelet Aggregation

Aggregation of platelets in 1 ml of fresh human platelet rich plasma (PRP) was monitored in a Born aggregometer.

The compound to be tested was added to the PRP at the

desired concentration, and the resulting mixture incubated at 37°C for 1 minute after which platelet aggregation was stimulated by the addition of adenosine diphosphate (ADP) to a concentration of 5 µM.

The anti-aggregatory effect of the compound was assessed by measuring the percentage inhibition of platelet aggregation in the presence of the compound as compared with when it was absent. The percentage inhibitions at various concentrations of hydantoin and prostaglandin E_1 (PGE_1) were established and compared to show activity compared to PGE_1.

Compound of Example No.	more or less polar diastereomer	Inhibition of Platelet Aggregation (X PGE_1)
3	less	0,25
	more	0,008
2	less	0,04
	more	0,01
6	less	0,04
	more	0,02
5	less	0,03
	more	0,008
1	less	<0,01
	more	<0,01

Example 13

Cardiovascular effects in rats

Male normotensive rats Wistar (Charles River) strain, (250 - 350 g) were anesthetised (chloroform) prior to cannulation to the left femoral vein and anaestesia maintained by intravenous chloralose (60 mg/kg). Pulsatile

blood pressure was recorded from the left femoral artery with an electronic transducer (Bell and Howell Type 4-327 L221) and integrated heart rate was measured with a cardiotachometer triggered from the arterial pressure waves.

The test compound (less polar diastereomer of the compounds of Example 2) was administered as a solution in physiological saline by intravenous injection via the femoral cannula. The responses recorded were allowed to return to the preinjection levels between successive administrations.

Injections of the vehicle alone in volumes equivalent to those containing drug did not produce hypotension.

The test compound showed less than one per cent of the hypotensive effect of prostacyclin.

Example 14

Tablet Formulation	In one tablet
Compound (less polar diastereomer of Example 3)	10,0 mg
Microcrystalline cellulose B.P.	200,0 mg
Starch B.P.	15,0 mg
Magnesium Stearate	1,0 mg

The compound is dissolved in a volatile solvent. (The compound is soluble in methanol and in ethanol.) The solution is then evenly distributed over the microcrystalline cellulose, and then blended with the starch and then with the magnesium stearate. The mixture is then pressed to tablets, each 226 mg in weight.

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Example 15

Capsule Formulation	In one capsule
Compound as used in Example 14	10 mg
Polyethylene glycol 4000	190 mg
Magnesium Stearate	1 mg

The polyethylene glycol is melted and the compound is stirred in, and the mixture cooled to room temperature. The wax produced is ground to give granules, which are mixed with the magnesium stearate and then filled into hard gelatine capsules containing 201 mg of mixture.

Example 16

1 µg/ml Injection

Compound (as used in Example 14	100 ug
Water for Injection	to ...100 ml

Dissolve the Compound in the Water for Injection. Sterilise the solution by filtration through a membrane filter, 0,22 um pore size, collecting the filtrate in a sterile receiver. Under aseptic conditions, fill the solution into sterile glass ampoules, 1 ml per ampoule; seal by fusion of the glass.

Example 17

10 µg/ml Injection

Compound (as used in Example 14)	1 mg
Ethyl Alcohol	10 ml
Propylene Glycol	30 ml
Water for Injection	to .....100 ml

Dissolve the Compound in the Ethyl Alcohol, add the

Propylene glycol and dilute to volume with Water for Injection.

Sterilise the solution by filtration through a membrane filter, 0,22 µm pore size, collecting the filtrate in a sterile vessel. Under aseptic conditions, fill the solution into sterile glass vials, 10 ml per vial. Close with a sterile rubber plug and secure with an aluminium collar.

Example 18

100 µg Single dose injection (freeze-dried)

Compound (as used in Example 14)	10,0 mg
Mannitol	2,5 g
N/10 Sodium Hydroxide Solution	qs to pH 10,0
Water for Injection	to ....100,0 ml

Suspend the Compound in approximately 20 ml Water. Add sufficient Sodium Hydroxide Solution to produce pH 10 and stir to dissolve the Compound. Add and dissolve the Mannitol and dilute to volume with Water for Injection.

Sterilise the solution by passage through a membrane filter, 0,22 um pore size, and distribute aseptically into sterile vials, 1 ml per vial. Freeze dry the solutions and seal the containers under aseptic conditions with rubber closures. Each vial contains 100 ug of Compound as its freeze-dried sodium salt.

Example 19

Suppository Formulation

Compound (as in Example 14)		3 mg
Massa Esterinum C	to	2 g

Melt the suppository base at about 40°C. Gradually incorporate the Compound and mix until homogeneous. Pour into suitable moulds and allow to set.

Massa Esterinum C is a commercially available suppository base consisting of a mixture of mono-, di- and tri-glycerides of saturated vegetable fatty acids. It is marketed by Henkel International, Dusseldorf.

Example 20

Soft Gelatine Capsule Formulation

Compound (as used in Example 14)		10 mg
Vehicle	about	100 mg

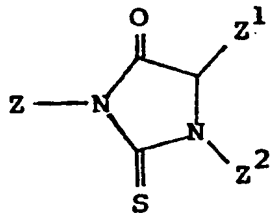
The compound is diluted into a suitable vehicle which will dissolve the compound and is then filled into soft gelatine capsules, each containing about 110 mg of mixture.

Example 21

By the method of Example 1 diethyl 2- (3-hydroxybutyl)-amino nonanedioate was converted to 5-(6-carboxyhexyl)-1-(3-hydroxybutyl)-2-thiohydantoin, two diastereomers: one- less polar- white crystalline solid, m.p. 92 - 95°C and the other- more polar- white crystalline solid, m.p. 102 - 104°C.

CLAIMS

1. A compound of formula (I)



(I)

in which Z is hydrogen or alkyl;
one of Z^1 and Z^2 is represented by the group $-CH_2-X-X^1-X^2$

wherein X is phenylene, $-C\equiv C-$, cis or trans $-CH=CH-$ or $-CH_2-CQ_2-$

in which each Q is independently selected from hydrogen and alkyl or the two Q's together from an alkylene radical having four, five or six carbon atoms;

X^1 is a covalent bond or a straight or branched alkylene chain having from 1 to 6 carbon atoms, optionally having one of any methylene groups replaced by an oxa (-O-) or thia (-S-) group, provided that at least one carbon atom separates such an oxa or thia group from a $-C\equiv C-$, $-CH=CH-$ or $-CO-$ group; and

X^2 is selected from 5-tetrazolyl, carboxyl, carboxamide,

-/2

hydroxymethylene, protected-hydroxymethylene and alkoxycarbonyl;

and the other of Z^1 and Z^2 is represented by the group $-Y-Y^1-Y^2-Y^3$,

wherein Y is $-CR_2-CH_2-$

in which each R is independently selected from hydrogen and methyl;

Y^1 is carbonyl, methylene, methylene substituted by hydroxyl or protected hydroxyl or methylene substituted by hydroxyl or protected-hydroxyl and by alkyl;

Y^2 is a covalent bond or a straight or branched alkylene chain having from 1 to 7 carbon atoms, optionally substituted on the carbon atom adjecent Y^1 by one or two groups each of which may be alkyl or a cyclic radical,

Y^3 is hydrogen, hydroxy, protected-hydroxyl, alkoxy having from 1 to 7 carbon atoms, a cyclic radical, phenyl, benzyl phenoxy or benzyloxy, wherein each of phenyl, benzyl, phenoxy and benzyloxy may be substituted in the benzene ring by one or more groups selected from hydroxyl, protected- hydroxyl, halogeno, nitro, amino, acylamino, alkenyl, alkoxy, phenyl and alkyl which may itself be substituted by one or more halogeno groups;

the cyclic radical in the definitions of Y^2 and Y^3 above being a radical derived by removal of a ring hydrogen atom from a monocyclic or polycyclic compound, other than benzene, having from 3 to 12 ring atoms selected from carbon, nitrogen, oxygen, and sulphur, which compound may be saturated or unsaturated and may be further substituted by one or more alkyl, fluoro, or fluorine-substituted alkyl groups;

or Y^2 and Y^3 together form an alkyl group, having from 1 to 7 carbon atoms, at least one hydrogen of which is replaced by fluoro;

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or Y is a covalent bond, $-CH_2-$, or $-CH_2.CH_2-$ and Y^1, Y^2 and Y^3 taken together form a cycloalkyl or bicycloalkyl group substituted by a hydroxyl or protected-hydroxyl group:

or a salt thereof.

2. A compound according to claim 1 in which Z^1 is $-CH_2-X-X^1-X^2$ and Z^2 is $-Y-Y^1-Y^2-Y^3$, wherein X, X^1, X^2, Y, Y^1, Y^2 and Y^3 are as defined in claim 1.

3. A compound according to claim 1 or 2 in which X is cis- or trans -CH=CH-.

4. A compound according to claim 1 or 2 in which X and X^1 together form an alkylene or alkenylene group of from 3 to 7 carbon atoms.

5. A compound according to any one of claims 1 to 4 in which X^2 is alkoxycarbonyl, carboxyl or a salt thereof.

6. A compound according to any one of claims 1 to 5 in which Y^1 is methylene, methylene substituted by hydroxyl or protected-hydroxyl, or methylene substituted by hydroxyl or protected-hydroxyl and by alkyl.

7. A compound according to any one of claims 1 to 6 in which Y^2 is a covalent bond and Y^3 is a cyclic radical which is a cycloalkyl radical of from 4 to 7 carbon atoms.

8. A compound according to any one of claims 1 to 6 in which Y^2 is a straight or branched alkylene chain having from 1 to 7 carbon atoms and Y^3 is hydrogen.

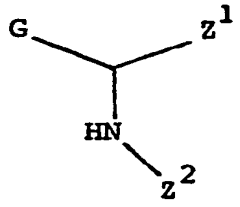
9. A diastereomer of a compound according to any one of the preceding claims which diastereomer is shown to be the less polar by thin layer chromatography using silica gel and a solvent system of chloroform: methanol : acetic acid in the proportions 90 : 5 : 5.

10. A compound according to any one of the preceding claims as an active agent for the treatment or prophyllaxis of a thrombo-embolic disorder in a mammal.

11. A pharmaceutical formulation comprising a compound according to any one of the preceding claims.

12. A process for preparing a compound according to any one of claims 1 to 8 which comprises

a) reacting a compound of formula (II),



(II)

wherein Z^1 and Z^2 are as defined for formula (I), and G is a carboxyl, alkoxycarbonyl, carboxamide or nitrile group; with thiocyanic acid, an alkylisothiocyanate, thiourea, nitrothiourea, or an N-alkylthiourea:

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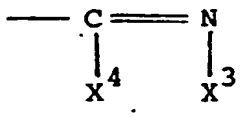
b) when X^2 in formula (I) is 5-tetrazolyl, reacting a compound of formula (I) but in which X^2 is defined as:



in which X^3 and X^4 together form a bond; or

X^3 is hydrogen or alkyl and X^4 is alkoxy, alkythio, $-NH.NH_2$, or amino; or

X^3 is hydroxa and X^4 is amino,

with nitrous acid or hydrazoic acid or a salt thereof, as appropriate to form a compound of formula (I) in which X^2 is 5-tetrazolyl:

c) when X^2 in formula (I) is hydroxymethylene, and/or when Y^1 in formula (I) is a -CHOH- group, reducing a compound of formula (I) in which X^2, as just defined, is replaced by carboxyl, carbonylhalide, acid anhydride group or an aldehyde and/or Y^1 is a carbonyl group:

d) when the compound of formula (I) contains a hydroxyl group, hydrolysing a compound of formula (I) in which the required hydroxyl group is, in the starting material, represented by a halo group:

e) when Y^1 in formula (I) is a carbonyl group oxidising a compound of formula (I) in which Y^1 is a -CHOH- group: or

f) when X in formula (I) is a -CH=CH- or a $-CH_2-CHQ-$ group (Q being as defined for formula (I)) hydrogenating a compound of formula (I) in which X is $-C\equiv C-$ or -CH=CQ-.

European Patent Office

EUROPEAN SEARCH REPORT

Application number
EP 78 10 1491

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	GB - A - 1 529 275 (BAYER) * Pages 1 and 2 * & FR - A - 2 322 865 & DE - A - 2 539 730 --	1
P/E	FR - A - 2 374 309 (BEECHAM) * Pages 2-6 and 12 and 13 * & BE - A - 861 956 & NL - A - 77 13971 & DE - A - 2 755 771 --	1,2,4, 5,6,7, 8,10, 11
P	FR - A - 2 362 839 (THE WELLCOME FOUNDATION) * Pages 1-3 * & NL - A - 77 06064 & BE - A - 855 337 & DE - A - 2 724 948 ----	1

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 233/86
403/00
A 61 K 31/41

TECHNICAL FIELDS SEARCHED (Int.Cl.³)

C 07 D 233/86
403/00

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	02-03-1979	DE BUYSER

EPO Form 1503.1 06.78

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 002 259**
A3

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 78101491.5

(22) Date of filing: 01.12.78

(51) Int. Cl.²: C 07 D 233/86
C 07 D 403/00, A 61 K 31/41

(30) Priority: 01.12.77 GB 5009377

(43) Date of publication of application:
13.06.79 Bulletin 79/12

(88) Date of deferred publication of search report: 27.06.79

(84) Designated contracting states:
BE CH DE FR GB IT LU NL SE

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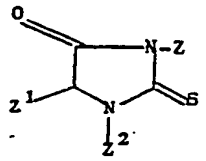
(54) **Hydantoin derivatives and salts thereof, their synthesis and intermediates, and pharmaceutical formulations.**

(57) Thiohydantoin derivatives with formula



wherein Z is hydrogen or alkyl
X is oxygen or sulfur
Z^1 and Z^2 represent the usual prostaglandin-chains, with pharmacological properties related to those of natural prostaglandins, intermediates therein, compositions containing the said derivatives, and their use in medicine. In particular, certain compounds have been found to be potent mimetics of the anti-platelet aggregatory properties of prostaglandin E_1.

EP 0 002 259 A3

European Patent Office

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P	FR - A - 2 362 839 (THE WELLCOME FOUNDATION) * Pages 1-3 * & NL - A - 77 06064 & BE - A - 855 337 & DE - A - 2 724 948	1	C 07 D 233/86 403/00

TECHNICAL FIELDS SEARCHED (Int.Cl.²)

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	02-03-1979	DE BUYSER